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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,390	04/27/2006	Abdullah I. Haj-Yehia	0-06-225/16799/US/03	8417

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EXAMINER	
CLARK, SARA E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,390	HAJ-YEHIA, ABDULLAH I.	
	Examiner	Art Unit	
	SARA E. CLARK	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-30,49 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-48* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/2005, 10/25/2007, 2/25/2008, 7/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

This application is a 35 U.S.C. 371 (national stage) of PCT/IL03/00878, filed 10/24/2003, which claims benefit of priority to provisional application 60/421,272, filed 10/25/2002. Claims 1-50, as amended, are pending.

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 31-48), and the species

- 11,17,21-trinitrato-16-DOXYL-dexamethasone (compound 12, specification p. 93), which reads on claims 31-48; and
- acute and chronic inflammatory conditions, which reads on claim 48,

in the reply filed on 3/23/2009 is acknowledged.

The traversal is on the ground(s) that the claimed compounds are novel and unobvious because the compounds taught by Garvey et al., as cited by the examiner in the restriction requirement dated 1/7/2009, do not comprise nitroxide radicals. This is not found persuasive because, as detailed in the restriction requirement, structural formulae recited in certain of the claims are not found in or common to all independent claims 1, 24, 26, 31, and 49. The shared technical feature of the independent claims is a compound described only in functional language – namely, a multifunctional steroid compound comprising at least one superoxide dismutase (SOD) mimic component and optionally at least one NO donor component – which, as disclosed in Garvey et al., is known. As recognized by MPEP §1850,

> In the case of independent claims to A + X and A + Y, unity of invention is present *a priori* as A is common to both claims. **However, if it can be established that A is**

> **known, there is lack of unity *a posteriori*, since A (be it a single feature or a group of features) is not a technical feature that defines a contribution over the prior art.**

Thus, where there is no common inventive concept amongst the groups of inventions that is novel, the claims lack unity of invention. The restriction requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-30 and 49-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/23/2009.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Claims 31-48 and the elected species are supported by the disclosure of provisional application 60/421,272, and are thus entitled to an effective filing date of 10/25/2002.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on 5/26/2005, 10/25/2007, 2/25/2008, and 7/16/2008 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Specification

5. The disclosure is objected to because of the following informalities: the elected compound 12 shown on page 93 of the specification is named 11,17,21-trinitrato-16-

DOXYL-dexamethasone. However, the structure indicates that C16 is substituted by a methyl group, while the DOXYL substituent is shown bonded to C20, creating a conflict between the structure and the name of the compound. The examiner has interpreted the structure to govern, and suggests that compound 12 is accurately named 11,17,21-trinitrato-20-DOXYL-dexamethasone, which is how it shall be referred to throughout. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 31-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for optical isomers and salts of the claimed compounds, does not reasonably provide enablement for their solvates. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. As recognized by MPEP 2164.01(a), "there are several factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." *In re Wands*, 8 USPQ2d 1400 (1988), sets out these factors, which include:

A. The Nature of the Invention. The nature of the invention is the wide range of nitric oxide-releasing steroid compounds encompassed by claim 31, and the optical isomers, salts, and solvates thereof.

B. The Breadth of the Claims. The breadth of claim 31 potentially includes a large genus of compounds, many of which are enabled; however, the recitation of "solvates" goes beyond the disclosure. Specifically, the instant claims encompass any solvate of the claimed compounds.

C. The State of the Prior Art and the Level of Predictability in the Art. Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization (see, e.g., Morissette et al., 2004, 56, 275-300).

Crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al., 2001, 3-26, abstract). In further discussing the predictability of the formation of solvates, Vippagunta et al. disclose that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be

made for a series of related compounds" (page 18, section 3.4). Therefore, for these reasons, the state of the art must be regarded as highly unpredictable.

D. The Amount of Direction or Guidance Present and Presence or Absence of Working Examples. No working examples are provided in the disclosure for the preparation of solvates, and the only guidance is for compounds of claim 31, as well as optical isomers, salts, and solvates thereof. The disclosure provides no direction or instruction for the preparation of solvates of compounds of claim 31. The specification only discloses that certain compounds can exist in solvated form; however, no specific compounds are identified as existing in this form or having been made in this form. Additionally, preferred embodiments and examples do not support enablement for solvates of *the claimed* compounds.

E. The Quantity of Experimentation Needed and the Level of Skill in the Art. While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare any solvate of the compounds of claim 31. The science of crystallization has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 31, 34-40, and 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjoeng et al. (US Pat. 5,707,984, published 1/13/1998) and Hsia (US Pat. 5,591,710, issued 1/7/1997), in view of Anggard et al. (WO99/37616, published 7/29/1999, provided by Applicant on the IDS dated 10/25/2007) and MacNee (Eur. J. Pharm. 429, 195–207, 2001).

Tjoeng et al. teach the modification of the 11- and 17- hydroxyl groups of the known steroid drug dexamethasone (9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-3*H*-cyclopenta[*a*]-phenanthren-3-one) to nitrate esters capable of releasing nitric oxide (NO) (abstract; formula (I), col. 4). Specifically, the elected compound 12 (11,17,21-trinatrato-20-DOXYL-dexamethasone), as recited in claims 31, 34-40, and 42-45, is identical to the compound of formula (I) taught by Tjoeng et al., where formula (I) has double bonds in the Δ^1 and Δ^4 positions, Q and R5 are hydrogen, R3 is methyl, P is fluorine, R6 is carbonyl, and R and R4 are nitrate esters, with the exception of the NO-donor and nitroxide free radical substituents at C20. Tjoeng et al. teach a carbonyl group and a second functional group bonded to C20, rather than –CH2-ONO2 and the nitroxide free radical DOXYL (4,4-dimethyl-3-oxazolinyloxy-) bonded to C20 as in elected compound 12. Tjoeng et al. also teach formula (I) as a pharmaceutical composition formulated with acceptable carriers or excipients (col. 6, lines 35-44), as recited by claims 46 and 47, for use in the treatment of inflammatory conditions (abstract), as recited by claim 48.

In summary, formula (I) of Tjoeng et al. differs from elected compound 12 only in the two substituents at C20.

Hsia teaches the N-substituted nitroxide free radical DOXYL (4,4-dimethyl-3-oxazolinyloxy-, col. 10, lines 32-42), and its addition to physiologically compatible compounds, as a component capable of mimicking the action of superoxide dismutase (SOD), i.e., scavenging reactive oxygen species (ROS), in the treatment of conditions associated with oxidative stress (abstract; col. 11, lines 9-17). The elected compound 12 is substituted at C21 by a third $-ONO_2$ and by DOXYL, as recited in claims 31, 34-40, and 42-45. However, Hsia teaches the incorporation of nitroxide free radicals into proteins rather than steroids (cols. 23-25), and does not teach the combination of a nitroxide free radical component with NO-releasing substituents into the same compound.

Anggard et al. teach compounds based on the nitroxide free radical PROXYL (2,2,5,5-tetramethylpyrrolidinyloxy free radical) as an ROS-scavenger, substituted with one or more $–ONO_2$ groups to confer nitric oxide (NO) releasing activity, for treatment of conditions associated with oxidative stress (p. 11). This provides the motivation to combine ROS-scavenging (nitroxide free radical) and NO-releasing ($-ONO_2$) functionalities into a single molecule, while the 11,17-ONO_2-dexamethasone of Tjoeng et al. provides the motivation to combine an NO-releasing component ($-ONO_2$) with an anti-inflammatory component (dexamethasone) into a single molecule.

MacNee teaches that oxidative stress plays an important role in the injurious and inflammatory responses in airways diseases such as asthma and COPD, linking

together the ROS-scavenging and anti-inflammatory functionalities (abstract). Taken together with the teachings of Hsia, Anggard et al., and Tjoeng et al., one of ordinary skill in the art would have been motivated to combine a nitroxide ROS-scavenging component and one or more NO-donor groups, known to alleviate oxidative stress, with a steroid known in the treatment of inflammation, because oxidative stress contributes to the pathogenesis of inflammation.

Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in treating acute or chronic inflammatory conditions with a compound combining the three functionalities taught by Tsjoeng et al. and Hsia rather than one or two alone, because NO-substituted steroids were known to alleviate inflammation, and nitroxide free radical groups were known ROS scavengers that reduce oxidative damage associated with inflammation.

10. Claims 32-33, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tjoeng et al. and Hsia, in view of Anggard et al. and MacNee, as applied to claims 31, 34-40, and 42-48 above, and further in view of Burrows et al. (US Pat. 5,610,149, issued 3/11/1997) and Lerner (US Pat. 2,437,261, issued 3/9/1948).

Burrows et al. teach steroid dimers linked at their C20 substituents by a six-carbon polyamine linker (formula II, abstract). However, a polyethylene glycol (PEG) linker is not taught.

Lerner teaches the linkage of multiple cholesteryl esters with PEGs of molecular weight from 1500 to 4000, overlapping the range of about 100 to about 4000 as recited in claim 33 (col. 4, lines 39-75). As recognized by MPEP §2144.05, it is *prima facie*

obvious to optimize quantitative variables such as molecular weight (MW) absent a showing that the claimed numerical quantity is a critical element of the invention:

> [g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

An advantage of linking two drug molecules together is to keep them in close proximity so as to increase their concentration at the target site, enhancing the therapeutic effect over the same dose that might be achieved if administered singly. Further, PEGs of various weights are commonly used linking molecules that are known to be nontoxic *in vivo*.

Because connecting steroidal compounds at their C20 substituents into a dimer was known, and using PEG linkers of MW 1500-4000 to connect steroidal compounds was known, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to enhance the efficacy of a drug by using PEG to link the C20 substituents of two molecules of the elected compound 12 (11,17,21-trinatrato-20-DOXYL-dexamethasone), as taught by Tjoeng et al., Hsia, and Anggard et al., with a reasonable expectation of success.

Conclusion

11. Claims 31-48 are rejected.

12. Any inquiry concerning this communication or earlier communications from the

examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SEC

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121